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Lung diseases directly associated with rheumatoid arthritis and their relation to outcome

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ABSTRACT

The outcome and cause of death of each lung disease directly associated with rheumatoid arthritis (LD-RA) has been poorly investigated.

We conducted a retrospective study of 144 patients with LD-RA in whom the median follow-up period after the initial visit for a respiratory examination was 4.5 years.

Fifty-seven patients were identified with usual interstitial pneumonia (UIP), 31 with bronchiectasis (BE), 16 with nonspecific interstitial pneumonia (NSIP), 11 with bronchiolitis, 5 with organizing pneumonia (OP), 5 with diffuse alveolar damage (DAD), and 19 with combined disease. The 5-year survival rates were 36.6% in the UIP group, 87.1% in the BE group, 93.8% in the NSIP group, 88.9% in the bronchiolitis group, 60.0% in the OP group, and 20% in the DAD group. Survival of patients with DAD was worse than that of patients with UIP. Overall survival of patients with UIP was worse than that of patients with BE, NSIP, or bronchiolitis. Of the 144 patients, 71 (49.3%) died, of whom 58 (81.7%) died due to respiratory lesions.

In patients with LD-RA, patients with DAD experienced the highest mortality, and survival of patients with UIP was worse than that of patients with NSIP.

KEYWORDS: bronchiectasis, bronchiolitis, diffuse alveolar damage, nonspecific interstitial pneumonia, rheumatoid arthritis, usual interstitial pneumonia

INTRODUCTION

Rheumatoid arthritis (RA) is a destructive, systemic inflammatory disorder. In addition to the impact RA has on the joints, pulmonary involvement occurs regularly and is responsible for a significant portion of the morbidity and mortality associated with RA [1]. Although pulmonary infection, drug toxicity, or both are frequent complications, lung disease directly associated with RA (LD-RA) is most common [1]. LD-RA includes interstitial lung diseases such as usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), and diffuse alveolar damage (DAD); airway diseases such as bronchiectasis (BE) and bronchiolitis; pleuritis; pulmonary vascular disease; and rheumatoid nodules [1, 2]. The prevalence of the different disease patterns of LD-RA was previously reported [2-6]: patterns specific to UIP, NSIP, OP, BE, and bronchiolitis were commonly seen on surgical lung biopsy and/or high-resolution computed tomography (HRCT), but DAD was quite uncommon. However, the difference in clinical features of patients with each type of disease has been poorly investigated.

Overall standardized mortality ratios of RA patients are reported as 1.27 to 2.26 [7, 8]. Excess mortality was seen in RA patients with infection, lymphoma, gastroenterologic disorder, cardiovascular disease, and pulmonary fibrosis [7, 8]. Causes of death in RA patients were cardiovascular disease in 31%, respiratory disease in 22%, solid tumors in 20%, cerebrovascular disease in 10%, and other reasons in 17% [8].

In the idiopathic interstitial pneumonias (IIPs), the histological pattern seen on surgical lung biopsy is the most important predictor of early mortality [9]. In LD-RA, the prognosis of UIP [2, 5, 10-12], NSIP [11, 12], OP [2], DAD [2], BE [13], bronchiolitis [5, 14], and

interstitial lung fibrosis [15] has been reported, but the relation between the individual disease types and outcome has not been fully investigated. Furthermore, whether the causes of death in patients with LD-RA are similar to those in all RA cohorts must be clarified. The aims of the present study were thus to retrospectively review RA patients with LD-RA, to document any differences in clinical features between the various disease types, to assess impact on prognosis, and to analyze causes of death.

METHODS

Study subjects

During the 10 years from April 1996 through March 2006, 277 patients with pleuropulmonary complications of RA were treated at our institution (Figure 1). Of these patients, 119 were not included because their lung disease, such as pulmonary infection, drug-induced pneumonia, or lung cancer, was not directly associated with RA. We excluded 7 patients with UIP because they had simultaneous lung cancer, 2 patients because pathological diagnosis obtained from surgical lung biopsy was unclassifiable interstitial pneumonia, and 5 patients because there were <5 patients with the same disease type. The remaining 144 patients comprised the cohort of this study. Patients were followed up through March 2009 or until death before March 2009. All patients fulfilled the revised criteria for RA of the American Rheumatism Association [16]. This study was approved by the institutional review board of Saitama Cardiovascular and Respiratory Center.

Diagnostic criteria of LD-RA

Diagnosis of LD-RA was based on the following criteria. Twenty-four patients were diagnosed based on histology (2 patients with BE were diagnosed by lobectomy, 14 by surgical lung biopsy, 3 by autopsy, and the remaining 5 by transbronchial biopsy), and 120 patients were diagnosed based on clinico-radiologic features. Pathological diagnosis of interstitial pneumonia obtained from surgical lung biopsy or autopsy was made using the consensus classification for idiopathic interstitial pneumonias [17]. In some patients with classic clinical and radiologic features of OP or DAD, diagnosis of these diseases was confirmed by the histologic pattern seen in a bronchoscopic biopsy specimen [17]. Follicular bronchiolitis (FB) was diagnosed when peribronchiolar prominent lymphoid follicles with germinal center were present [18]. Bronchiolitis obliterans (BO) or constrictive bronchiolitis was diagnosed if there was pathological evidence of a bronchiolar luminal narrowing or occlusion by scarring [18]. Pathologic diagnoses in 24 patients included UIP in 3; NSIP in 4; OP in 2; DAD in 3; FB in 1; BO in 1; FB and BO in 3; BE in 2; OP and FB in 2; UIP and FB in 1; UIP, NSIP, and FB in 1; and UIP, OP, and pleuritis in 1. Standard high-resolution computed tomography (HRCT) protocols were used to obtain images for evaluation. Collimation was less than 2.0 mm in all images, and all were reconstructed using high-resolution algorithms. CT scans were obtained at suspended end-inspiratory effort with the patients in the supine position. The scans were reviewed independently in a blinded fashion by two observers (N.T. and N.S.) and were interpreted on the basis of previously published data [4, 6]. Scans consistent with UIP contained predominant basilar reticulation, traction bronchiectasis, and honeycombing. Scans consistent with NSIP contained predominant bibasilar ground-glass attenuation with limited

reticulation and were absent of honeycombing. Scans consistent with OP contained patchy airspace consolidation associated with ground-glass attenuation. Scans consistent with DAD contained patchy or diffuse ground-glass attenuation associated with airspace consolidation and may have shown intralobular reticulation or traction bronchiectasis. Scans consistent with bronchiolitis contained centrilobular and/or peribronchial nodules, branching linear structures, and mosaic perfusion with bronchial dilatation. Each observer noted the most appropriate diagnosis for each patient. In cases of disagreement, consensus was obtained following further review.

DAD was distinguished from acute exacerbation of UIP, which was included in UIP [19]. Because FB and BO can coexist in the airways [14], they were regarded together as bronchiolitis. Some patients with combined disease were included into the Combined group. Patients who had UIP and BE together were not considered as having traction bronchiectasis caused by UIP but as having BE limited to 1 or multiple lobes.

Study design

Case records of 144 patients with LD-RA were retrospectively reviewed. The following data were recorded: age at onset of RA, age at onset of LD-RA, smoking history, RA drug before the onset of LD-RA, laboratory findings, blood gas analysis, pulmonary function test results, treatment of LD-RA for each patient group, and number and causes of death. We analyzed both the existence of any differences in clinical features and prognosis between the various disease groups and causes of death.

Statistical analysis

Weighted κ coefficients of agreement (κ_w) were calculated for diagnosis data to quantify observer variation. The weights reflect a partial match for multiple disease diagnoses. Categorical baseline characteristics are summarized by frequency and percent, and continuous characteristics are reported as mean ± standard deviation. To investigate risk factors of each disease, baseline characteristics were compared by Fisher's exact test or Kruskal-Wallis test in accordance with nominal and continuous variables, respectively. Survival probability of each patient group was estimated by the Kaplan-Meier method and compared by global log-rank test. Cox regression analysis was used to examine the hazard ratio (HR) between UIP (the reference disease) and other disease groups. In all analyses, p values <0.05 were considered to be statistically significant.

RESULTS

Baseline patient clinical characteristics and demographics

Baseline clinical characteristics and demographics are shown in Table 1. Of the 19 (13.2%) patients who developed LD-RA before RA onset, 11 had UIP, 4 had NSIP, 3 had bronchiolitis, 2 had BE, and 1 had OP. Corticosteroids were used in 82 patients. Median follow-up period after the initial visit for a respiratory examination was 4.5 years (range 0-24 years).

Patient characteristics and test findings by disease type

Patient characteristics, laboratory findings, and blood gas analysis and pulmonary function test results by disease type are shown in Table 2. There was good agreement between the observers regarding radiological diagnosis ($\kappa_{w,}$ 0.718, 95% confidence interval (CI); 0.685-0.751). UIP, OP, and DAD were more likely to be seen in men and smokers. BE was more common in patients with younger onset of RA, longer period from RA onset to LD-RA diagnosis, and in those not using corticosteroids. In UIP or DAD patients, LDH, CRP, and A-a DO_2 values were higher. Elevation of Krebs von den Lungen-6 (KL-6) values was more likely to be seen in UIP, DAD, NSIP, or bronchiolitis. Elevation of $PaCO_2$ values was more likely to be seen in bronchiolitis.

Histopathology and HRCT pattern

All patients with histopathology of UIP, NSIP, DAD, and BE had the same HRCT pattern (Figure 2). Of the 2 patients with histopathology of OP, 1 had OP pattern and the other had OP and BE pattern on HRCT. Of the 5 patients with histopathology of bronchiolitis, 4 had bronchiolitis pattern and 1 had NSIP pattern on HRCT. Five patients with combined disease had one or two HRCT patterns of the combined disease.

Treatment of LD-RA for each patient group

Of the 57 UIP patients, 44 underwent no treatment, 8 received 10-30 mg/day prednisolone, and 4 underwent steroid pulse therapy with subsequent administrations of oral prednisolone. Two of these 4 patients had simultaneous methotrexate pneumonitis, and 2 had acute exacerbations of UIP. In addition, 15 of the untreated patients subsequently

experienced acute exacerbations and took steroid pulse therapy at that time. Patients with BE were provided with supportive care.

Three of the 16 NSIP subjects were treated with steroid pulse therapy and subsequent oral prednisolone therapy: 3 with oral prednisolone 30-50 mg/day, and 1 with prednisolone 30 mg/day plus cyclosporine. The others were merely observed and received no medications. Three of the 5 OP patients were administered oral prednisolone 10-30 mg/day, and the others were only observed. Six of the 11 patients with bronchiolitis underwent macrolide therapy, and 1 patient received oral prednisolone 30 mg/day. The remaining 4 patients underwent observation only. All 5 DAD patients were treated with corticosteroid pulse therapy and cyclophosphamide. Of the 19 patients with combined disease, 5 took 20-50 mg/day of oral corticosteroids, 5 were given macrolide therapy, 1 underwent steroid pulse therapy, and 8 were observed but given no medication.

Survival rates and causes of death

Survival rates are presented in Table 3. Of the 144 patients, 71 (49.3%) died. Fifty-eight (81.7%) died due to respiratory lesions. Median survival time of all LD-RA patients was 8.1 years, 5-year survival rate was 60.1%, and 10-year survival rate was 46.0%. Median survival rates by LD-RA were UIP, 3.9 years; bronchiolitis, 9.3 years; NSIP, 17 years; and DAD, 0.2 years. Five-year survival rates were UIP, 36.6%; BE, 87.1%; NSIP, 93.8%; OP, 60.0%; bronchiolitis, 88.9%; and DAD, 20%; and 10-year survival rates were UIP, 24.6%; BE, 81.7%; NSIP, 93.8%; OP, 60.0%; bronchiolitis, 47.4%; and DAD, 0%.

Estimated survival times between the 7 RA-LD groups differed with statistical significance ($p<0.001$) (Figure 3). Survival time of patients with DAD was significantly worse than that of patients with UIP (HR=2.892). Survival times of patients with BE (HR=0.158), NSIP (HR=0.116), or bronchiolitis (HR=0.247) were significantly better than that of the patients with UIP (Table 4).

Causes of death in UIP patients were acute exacerbations (*n*=15), chronic progressions (*n*=9), lung cancer (*n*=5), pneumonia (*n*=5), or other reasons (*n*=11). Causes of death are summarized in Table 3.

DISCUSSION

We clinicopathologically investigated LD-RA including UIP, NSIP, OP, DAD, BE, bronchiolitis, and combined disease to determine differences in clinical features especially in relation to prognosis and causes of death in RA patients with these diseases. Of the 7 disease entities, survival rate of patients with DAD was the shortest, and survival of patients with NSIP the longest, in comparison to patients with UIP. More than 80% of the patients with LD-RA died from pulmonary diseases.

Lee et al. reported that males and smokers more frequently have RA-associated UIP [11]. In the present study, UIP was more likely to be seen in men and smokers. Some reports indicate that BE complicated by RA is frequent in nonsmokers [20]; however, other reports show no significant difference [21]. In addition, one report showed that BE was the precedent in 30 (94%) of 32 patients before RA onset [21], whereas another report

suggested that BE was the precedent in 5 of 23 RA patients [22]. BE was confirmed before RA onset in only 2 of our 31 patients with BE.

Elevation of KL-6 level is known to occur in patients with interstitial pneumonia, hypersensitivity pneumonitis, and pulmonary alveolar proteinosis. Kinoshita et al. reported that KL-6 level in patients with advanced RA/UIP can rise to more than 1000 U/ml but does not elevate in patients with airway disease or OP [23]. In the present study, KL-6 elevation was observed in patients with UIP, DAD, NSIP, and bronchiolitis.

Median survival time of our patients with UIP was 3.9 years. In general, median survival time of patients with idiopathic pulmonary fibrosis (IPF) is 2-4 years [9, 17]. Flaherty et al. compared 99 IPF and 9 UIP patients (including 4 with RA/UIP) with complications of collagen vascular disease (CVD) [24]. The prognosis of CVD/UIP is better than that of IPF because less fibrotic foci are present histopathologically in CVD/UIP [25]. In contrast, median survival time of patients with RA/pulmonary fibrosis reported by Hakala is 3.5 years, which is similar to our findings [15]. Park et al. [10] and Kim et al. [12] found no difference in prognosis between IPF and RA/UIP. Moreover, Song et al. reported that in UIP associated with CVD, patients with RA/UIP have the gravest prognosis [26]. Further accumulation of data is required to adequately compare prognosis between IPF and RA/UIP.

It was reported that 5- and 10-year survival rates of patients with idiopathic NSIP were 82.3% and 73.2%, respectively [27]. No fatal cases of RA/NSIP were reported by Lee et al. [11]. In our study, 5- and 10-year survival rates for RA/NSIP were both 93.8%, and there were no fatal cases owing to respiratory disease.

DAD is not frequent in LD-RA, occurring in only 1 (1.5%) of 67 cases in the CT review from Tanaka et al. [4] and in 2 (5%) of 40 cases of open lung biopsy from Yousem et al. [2]. Of our 144 patients, 5 (3.4%) had DAD. The mortality rate of idiopathic DAD is high (≥50%), with most deaths occurring between 1 and 2 month after onset of illness [16]. Few reports address the prognosis of RA/DAD. Yousem et al. reported that 1 of 2 patients died from DAD, and the other improved [2]. Parambil et al. reported 5 patients with RA/DAD. Four had preexisting RA-associated interstitial lung disease, and 1 had pure DAD; only this patient survived [28]. In our 5 patients, 3 died of respiratory failure due to DAD early after hospital admission.

The 5-year mortality rate of cryptogenic OP is generally 5% [9]. In one report, 2 of 6 RA/OP patients died: 1 from primary disease and the other from other disease [2]. Although 2 of our 5 OP patients died, the individual causes of death were pneumonia and malignant lymphoma and not OP itself. The prognosis of OP might be as good as that of cryptogenic OP.

The 10-year survival rate of our RA/BE patients was 81.7%. Swinson et al. reported that the 5-year survival rate of their RA/BE patients was 68.8%. Mortality was higher than that of the general population or for RA or BE alone [13]. Shadick et al. reported a mortality rate of 17.4% in 23 RA/BE patients [22]. In the 5 fatal cases of RA/BE in the present study, acute exacerbations or pulmonary infections accounted for 80% of the causes of death. Infection control would be beneficial for improvement of the prognosis.

The 5-year survival rate of our RA/bronchiolitis patients was 88.9%, but the 10-year survival rate decreased to 47.4%. BO often presents with severe respiratory failure and is

resistant to treatment. Therefore, the prognosis is particularly poor [29]. Devouassoux et al. define patients with obliterative bronchiolitis in RA as those with a forced expiratory volume in 1 second/forced vital capacity of <50% and/or residual volume/total lung capacity of >140% [30]. They followed up 25 patients for an average of 48.2 months, during which time 4 (16%) patients died and 40% lapsed into chronic respiratory failure. Hayakawa et al. suggested that erythromycin may be useful for the management of RA/bronchiolitis [14]. Six of our 11 RA/bronchiolitis patients received erythromycin or clarithromycin, and cough and sputum production decreased in 5 of these patients. A prospective study is required to further prove the efficacy of these drugs.

Hakara et al. reported that 80% of RA/lung fibrosis patients died of progression of primary lung disease, and only a few patients died of lung cancer, pulmonary tuberculosis, or cardiovascular disease [15]. Lee et al. reported that 5 of 10 patients with RA/UIP died. Causes of death consisted of exacerbation in 1 patient, pulmonary infection in another, and steady progression of lung disease in the remaining 3 [11]. In our study, 58 of 71 patients (81.7%) died of respiratory complications. In comparison with a report indicating that 22% of RA patients died from respiratory complications [8], our results would indicate that the death rate from pulmonary complications is higher in patients with LD-RA than in patients with RA alone.

One limitation of the present study is that the diagnosis in a large number of the patients was not proven pathologically. However, if only patients diagnosed pathologically are included in a study, those patients with a distinctive radiographic pattern of UIP are likely not to undergo surgical lung biopsy, and these patients might be excluded from the study.

The pattern of radiographic abnormalities seen on HRCT in RA has proved to be an excellent predictor of the underlying pathological pattern [1]. In addition, our κ_w results in regard to radiological diagnosis were good, and among the patients whose histopathology results were available, all patients with HRCT patterns of UIP, NSIP, DAD, or BE had the same histology. The present study includes many patients who were diagnosed with the aid of imaging tools; however, we believe there are few inaccuracies in the diagnosis of the clinical disease entity. The other limitation concerns the possibility of diagnostic delay because our hospital is a specialized cardiovascular-respiratory hospital, and the patients who had been followed by other rheumatologists were not admitted to our hospital until a respiratory symptom appeared. The majority of LD-RA occurs within the first years after the initial diagnosis [1]. Our UIP subjects were diagnosed at an average of 7.5 years after RA onset. This delay in diagnosis might affect median or 5-year survival rates.

In summary, the mortality rates were different among disease groups. Patients with DAD experienced the highest mortality, and with UIP as the reference disease, the HR was estimated to be 2.892 with 95% CI=[1.134, 7.736]. In contrast, the NSIP group experienced the lowest mortality (HR=0.116, 95% CI=[0.028, 0.477]), and this was significantly lower than that of the UIP group. More than 80% patients with LD-RA died of pulmonary disease. Thus, establishment of effective treatment for each LD-RA and improvement in treatment outcome for patients with pulmonary infections are necessary.

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TABLE 1 Characteristics of patients with lung disease directly associated with rheumatoid arthritis (LD-RA)

Characteristic	Value
Age, years (range)	65.2±9.8 (34-88)
Sex, male/female	60/84
Smoking status	
Current + former	54
Never	90
Smoking, pack-years	16.6±28.1 (0-120)
Age at RA, years	55.4±14.5 (18-82)
Age at LD-RA, years	65.2±9.8 (34-88)
Duration of RA, years	9.7±12.0 (-15-57)
Combined disease	
2 diseases	
UIP + BE	3
UIP + Bronchiolitis	2
BE + Bronchiolitis	8
Bronchiolitis + OP	2
3 diseases	
UIP + NSIP + Bronchiolitis	1
UIP + OP + Pleuritis	1
BE + Bronchiolitis + OP	1
Bronchiolitis + OP + Pleuritis	1

RA: rheumatoid arthritis; UIP: usual interstitial pneumonia; BE: bronchiectasis; OP: organizing pneumonia; NSIP: nonspecific interstitial pneumonia.

TABLE 2. Background, laboratory findings, blood gas analyses, and pulmonary function tests of each patient group with lung disease directly associated with rheumatoid arthritis (LD-RA)

	UIP	BE	NSIP	Bronchiolitis	OP	DAD	Combined	p-value
Sex, male/female	33/24	4/27	6/10	2/9	4/1	4/1	7/12	<0.001
Age at RA, yrs	60.2±12.8	46.2±14.3	52.3±12.5	50.8±11.6	63.8±8.2	59.4±12.9	58.1±16.8	<0.001
Age at LD-RA, yrs	67.7±9.4	61.7±10.5	61.3±6.9	62.4±8.7	64.8±9.5	65.2±7.8	68.3±11.1	0.016
Duration of RA, yrs	7.5±11.6	15.5±12.9	9.1±13.2	11.5±14.9	1±2	5.8±8.3	10.2±11	0.029
Smoker/non-smoker	29/28	5/26	7/9	1/10	3/2	3/2	6/13	0.005
Smoking, pack-yrs	25.8±35.4	4.7±12.1	13.3±20.9	1.2±4.1	24.8±22.7	32±30.3	14.8±26.2	0.003
Steroid use, yes/no	41/16	10/21	8/8	7/4	2/3	3/2	11/8	0.021
DMARDs use, yes/no	38/19	20/11	12/4	9/2	4/1	2/3	12/7	0.749
WBC (/μl)	10130±5243	9142±4428	8638±3458	8564±3558	6500±1012	13080±3813	8531±2415	0.097
LDH (U/l)	439±598	225±80	274±108	256±90	176±26	743±42	245±108	<0.001
CRP (mg/dl)	8.4±8.4	5.6±7.5	5.2±8.4	2.3±3.3	7.2±1.7	17.2±15	4.5±6.7	0.008
ESR (/mm)	77.7±37.4	62±35.3	63.2±31.2	63.1±44	77.3±29.5	81±17.5	69±38	0.416
RF (IU/ml)	509±1068	224±354	242±563	317±369	439±434	946±984	8221±2402	0.672
KL-6 (U/l)	797±588	299±104	783±1095	770±700	367±191	1158±350	411±187	<0.001
PaO_2 (Torr)	65.2±14.1	73.1±14.2	83±13.4	70±15.3	77.8±7.5	45.7±10.4	70±13	0.003
$PaCO_2$ (Torr)	36.9±4.5	37.2±4.6	40.3±2.9	45.5±5.6	40±6.1	30.7±5.3	40±8.4	0.004
A-aDO_2 (Torr)	39±17	30±13	17±14	23±13	29±24	66±16	30±17	0.001
%VC (%)	70.4±18	79.9±18.9	76.2±14.2	75.9±20.6	71±21.8	65.4±3.3 (n=2)	75±18	0.519
FEV1% (%)	80.1±10	86.2±14.6	80.7±10	69.6±12.3	82±15.4	78.8±2.6 (n=2)	78±15	0.059
%DLCO (%)	78.9±13.9	86.8±14.6	79.1±11.1	92.4±15.8	85.8±21.1	77.2±4.0 (n=2)	85±12	0.172

UIP = usual interstitial pneumonia, BE = bronchiectasis, NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia, DAD = diffuse alveolar damage, RA = rheumatoid arthritis, DMARDs = disease modifying antirheumatic drugs. ESR = erythrocyte sedimentation rate, RF = rheumatoid factor, KL-6 = Krebs von den Lungen-6. Pulmonary function test data of 3 DAD patients were not available.

TABLE 3. Survival and causes of death in patients with lung disease directly associated with rheumatoid arthritis

	UIP	BE	NSIP	Bronchiolitis	OP	DAD	Combined	Total
Number of patients	57	31	16	11	5	5	19	144
Median survival, yrs	3.9	-	17	9.3	-	0.2	8	8.1
5-year survival	36.6%	87.1%	93.8%	88.9%	60.0%	20.0%	59.2%	60.1%
10-year survival	24.6%	81.7%	93.8%	47.4%	60.0%	0.0%	38.9%	46.0%
Total deaths, No (%)	45 (78.9%)	5 (16.1%)	2 (12.5%)	3 (27.3%)	2 (40.0%)	5 (100%)	9 (47.4%)	71 (49.3%)
Cause of death								
Acute exacerbation of UIP	15	0	0	0	0	0	4	19
Acute exacerbation of BE	0	2	0	0	0	0	1	3
Disease progression	9	0	0	1	0	3	0	13
Pneumonia	5	1	0	1	1	0	1	9
Other pulmonary infections	3	1	0	0	0	0	0	4
Lung cancer	5	1	0	0	0	0	0	6
Pneumothorax	1	0	0	1	0	0	0	2
Drug-induced pneumonitis	1	0	0	0	0	0	0	1
Radiation pneumonitis	1*	0	0	0	0	0	0	1
Non-respiratory disease	5	0	2	0	1	2	3	13

UIP = usual interstitial pneumonia, BE = bronchiectasis, NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia, DAD = diffuse alveolar damage. Radiation pneumonitis was due to irradiation for esophageal cancer.
Global log-rank test: $p<0.001$

TABLE 4. Comparison of survival between patient groups by Cox model

	Cox proportional hazards regression analysis		
	Hazard ratio	95% CI	p-value
DAD vs UIP	2.892	1.134 - 0.376	0.026
BE vs UIP	0.158	0.063 - 0.400	<0.001
NSIP vs UIP	0.116	0.028 - 0.477	0.003
OP vs UIP	0.353	0.085 - 1.462	0.151
Bronchiolitis vs UIP	0.247	0.077 - 0.799	0.020
Combined vs UIP	0.501	0.244 - 1.030	0.060

CI = confidence interval, DAD = diffuse alveolar damage, UIP = usual interstitial pneumonia, BE = bronchiectasis, NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia.

Figure Legend

FIGURE 1. Flow diagram of patients with lung disease directly associated with rheumatoid arthritis (LD-RA).

Abbreviations: RA: rheumatoid arthritis; UIP: usual interstitial pneumonia; BE: bronchiectasis; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; DAD: diffuse alveolar damage; IP: interstitial pneumonia; DIP: desquamative interstitial pneumonia; LPD: lymphoproliferative disorder.

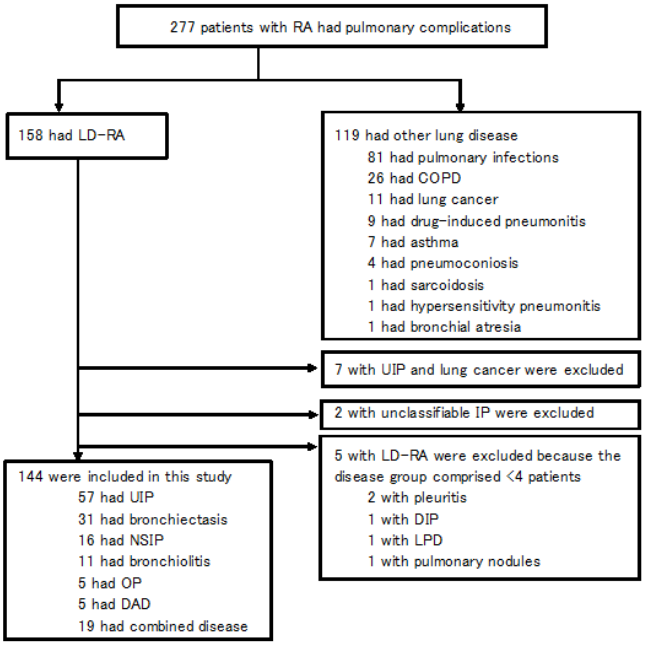

FIGURE 2. Flowchart of histopathologic and HRCT patterns in patients with lung disease directly associated with rheumatoid arthritis.

Abbreviations: UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; DAD: diffuse alveolar damage; BE: bronchiectasis; BO: bronchiolitis obliterans; FB: follicular bronchiolitis.

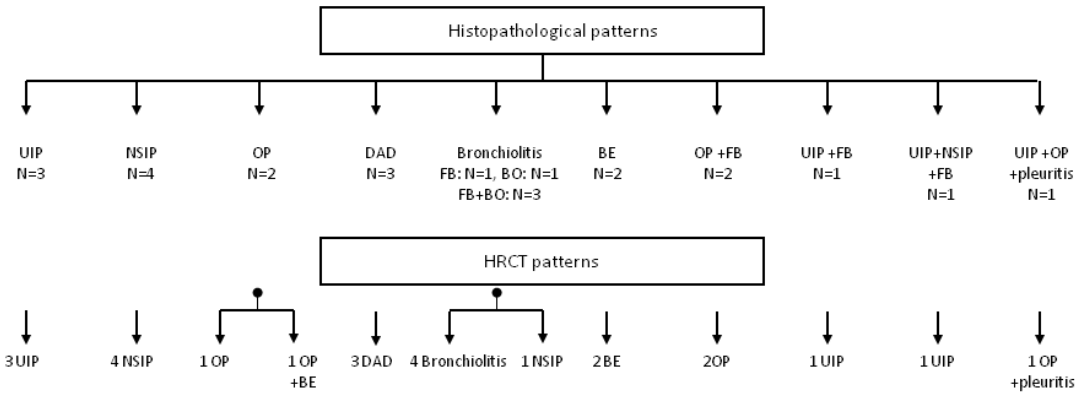

FIGURE 3. Comparison of Kaplan-Meier survival curves between patient groups. Abbreviations: BE: bronchiectasis; DAD: diffuse alveolar damage; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; UIP: usual interstitial pneumonia.